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ALLEGRO project

Development of NTCP models for head and neck cancer patients treated with three-dimensional conformal radiotherapy for xerostomia and sticky saliva: The role of dosimetric and clinical factors

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ABSTRACT

Purpose: The purpose of this multicentre prospective study was to investigate the significance of the radiation dose in the major and minor salivary glands, and other pre-treatment and treatment factors, with regard to the development of patient-rated xerostomia and sticky saliva among head and neck cancer (HNC) patients treated with primary (chemo-) radiotherapy ((CH)RT).

Methods and materials: The study population was composed of 167 consecutive HNC patients treated with three-dimensional conformal (3D-CRT) (CH) RT. The primary endpoint was moderate to severe xerostomia (XER6m) as assessed by the EORTC QLQ-H&N35 at 6 months after completing (CH)RT. The secondary endpoint was moderate to severe sticky saliva at 6 months (STIC6 m). All organs at risk (OARs) potentially involved in salivary function were delineated on planning-CT, including the parotid, submandibular and sublingual glands and the minor glands in the soft palate, cheeks and lips. Patients with moderate to severe xerostomia or sticky saliva at baseline were excluded. The optimum number of variables for a multivariate logistic regression model was determined using a bootstrapping method.

Results: The multivariate analysis showed the mean parotid dose, age and baseline xerostomia (none versus a bit) to be the most important predictors for XER6m. The risk of developing xerostomia increased with age and was higher when minor baseline xerostomia was present in comparison with patients without any xerostomia complaints at baseline. Model performance was good with an area under the curve (AUC) of 0.82.

For STIC6m, the mean submandibular dose, age, the mean sublingual dose and baseline sticky saliva (none versus a bit) were most predictive for sticky saliva. The risk of developing STIC6 m increased with age and was higher when minor baseline sticky saliva was present in comparison with patients without any sticky saliva complaints at baseline. Model performance was good with an AUC of 0.84.

Conclusions: Dose distributions in the minor salivary glands in patients receiving 3D-CRT have limited significance with regard to patient-rated symptoms related to salivary dysfunction. Besides the parotid and submandibular glands, only the sublingual glands were significantly associated with sticky saliva. In addition, reliable risk estimation also requires information from other factors such as age and baseline subjective scores. When these selected factors are included in predictive models, instead of only dose volume histogram parameters, model performance can be improved significantly.

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In patients with head and neck cancer (HNC), radiotherapy includes irradiation of parts of the salivary glands. This might result in salivary dysfunction and subsequent xerostomia, which is one of

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the most frequently reported side effects of radiation treatment in the head and neck area [1–6]. In addition, salivary dysfunction may lead to additional effects, such as sensation of a dry mouth, altered taste, swallowing problems and speech problems which have a significant impact on the general dimensions of health-related quality of life (HRQoL) [1,7–15].

Content and production of saliva may differ between different salivary glands and different time points [16–22]. The parotid and submandibular glands are responsible for the main stimulated saliva production and the production of saliva at rest, while during sleep saliva is predominantly produced by the sublingual and the minor salivary glands located at the inner surface of the lower lip, upper lip and both cheeks and the submandibular glands [18]. In contrast, during sleep the saliva production of the parotid glands declines almost to zero.

Until now, most investigators mainly focused on the univariate relationship between parotid gland dose and stimulated and/or unstimulated parotid salivary flow [23–25]. However, the development of xerostomia as reported by patients most likely depends on a variety of prognostic factors, such as radiation dose distributions in the salivary glands as well as demographic, tumour-related and treatment-related factors [26]. Therefore, large prospective cohort studies are required to determine which factors are most important in predicting patient-rated xerostomia after a curative course of radiation in which all these factors can also be taken into account.

The study reported on in this paper is part of the ALLEGRO project (early and late health risks to normal/healthy tissues from the use of existing and emerging techniques for radiation therapy) which is funded by the European Union [27]. The three general objectives of the ALLEGRO project are: (1) investigation of the magnitude and distribution of radiation doses in normal tissues (from all causes, adjusted where necessary for biological effect) received in treatments with current and emerging radiation technologies; (2) investigation of the risk of second cancers from the radiation exposure of normal tissues, and: (3) modelling of the risk of normal tissue damage in common cancer treatments and estimation of the beneficial effects of emerging radiation delivery techniques (e.g., radiation with protons).

In the work package regarding normal tissue complication probability (NTCP) modelling, a 4-step approach is applied. Step 1 includes the development of predictive models among patients treated with 3D conformal radiotherapy (3D-CRT). In step 2 the validity of these predictive models will be tested among patients treated with intensity modulated radiotherapy (IMRT). In step 3, we will investigate as to whether new radiation techniques could be further optimized in terms of physical dose distributions using the most relevant dose volume histogram (DVH) parameters from the predictive models from steps 1 and 2, also referred to in silico planning comparative (ISPC) studies. Finally, the aim is to estimate the potential benefit of these new techniques by combining the results of the predictive models and the ISPC-studies in order to see if, and to what extent, differences in physical dose distributions translate into reductions in NTCP-values.

The main objective of the current paper was to report on the results of the first step, i.e., the development of predictive models for patient-rated symptoms related to salivary dysfunction (i.e., xerostomia and sticky saliva) taking into account dose distributions in all salivary glands (i.e., major as well as minor salivary glands) as well as taking into account other potential clinical and treatment-related determinants.

Methods and materials

The standardised follow up program

Since 1997, all patients referred for radiotherapy for HNC to the Department of Radiation Oncology of the VU University Medical Center, Amsterdam, the Netherlands (VUMC) were included in a standardised follow up program (SFP). Since March 2007, the same SFP was established at the department of Radiation Oncology of the University Medical Center Groningen, Groningen, The Nether-

lands (UMCG). Until the end of 2007, the majority of patients were treated with 3D-CRT, while since 2008 patients were increasingly treated with IMRT. The SFP includes a prospective evaluation of toxicity and HRQoL on a routine basis, prior to, during and at regular intervals after curative (chemo-) radiotherapy ((CH)RT). HRQoL was assessed using the EORTC QLQ-C30 and the additional head and neck cancer module, the EORTC QLQ-H&N35 at baseline, 6 weeks post-treatment and at 6 month intervals thereafter [28–30].

Patients

To be included in the analysis, patients had to fulfil the following eligibility criteria: (1) HNC originating in the oral cavity, oropharynx, larynx, hypopharynx or nasopharynx; (2) treated with curative 3D-CRT either alone or in combination with chemotherapy or cetuximab; (3) no previous surgery, radiotherapy and/or chemotherapy; (4) no previous malignancies; (5) no distant metastases; (6) planning-CT and 3D-dose distributions available in DICOM-format, and: (7) HRQoL assessments available prior to and 6 months after completion of (CH)RT. Eventually, the prospective cohort used for this analysis was composed of 205 patients who fulfilled all these eligibility criteria.

Endpoints

For the evaluation of patient-rated xerostomia and sticky saliva, the EORTC QLQ-H&N35 questionnaire was used 6 months after treatment. Six months was chosen because former studies indicated that after 3D-CRT the assessment on this time point is predictive for subsequent time points [5,11,31]. For all questions, including those regarding xerostomia and sticky saliva, a 4-point Likert scale was used varying from none, a bit, quite a bit and a lot. For the purpose of this study, the primary endpoint was defined as moderate to severe xerostomia at 6 months after completion of radiotherapy, which corresponds with the two highest scores on the 4-point scale. Patients with moderate to severe xerostomia or sticky saliva at baseline were excluded from the analysis. This was done, as we were primarily interested in xerostomia and sticky saliva induced by radiation treatment itself. Thirty-three patients suffered from moderate to severe xerostomia at baseline and were excluded for further analysis. From these 172 patients, 165 (96%) completed the EORTC QLQ HN35 at 6 months after treatment and were included in the analysis.

Similarly, for the analysis of sticky saliva, only those with no or minimal complaints at baseline were included. Twenty-eight of all 205 included patients suffered from moderate to severe sticky saliva and were excluded from further analysis. From the remaining 177 patients, 167 (94%) completed the EORTC QLQ-HN35 at 6 months after treatment.

The majority of patients were males (76%) and the mean age of the study population was 63.8 years, ranging from 41 to 92 years for patients included in both the xerostomia and sticky saliva analyses. Most of the patients were treated with radiotherapy alone (78%). The demographic and tumour characteristics of these two study populations are listed in Table 1.

Treatment

Radiotherapy was delivered using megavoltage equipment (6 MV linear accelerator). In all patients, a planning CT scan was made in supine position. All patients were treated with 3D-CRT, without attempts to spare the salivary glands. Patient position was fixed with a five point individual thermoplastic mask (Posicast® thermoplastics, CIVCO) in combination with a standard head support (Posifix® supine headrest, CIVCO). Position verification

Table 1Demographic and disease-related characteristics for the patients included in the xerostomia (165) and sticky saliva analysis ($n = 167$).

Characteristics	Xerostomia (n = 165)	%	Sticky saliva (n = 167)	%
Sex				
Male	126	76	124	74
Female	39	24	43	26
Age				
<65	101	61	99	59
>65	64	39	68	41
Chemotherapy				
Yes	36	22	36	22
No	129	78	131	78
Tumour classification				
T0	5	3	6	4
T1	27	16	28	17
T2	85	52	87	52
T3	25	15	22	13
T4	23	14	24	14
Node classification				
N0	113	69	118	70
N1	10	6	9	5
N2a	5	3	5	3
N2b	17	10	16	10
N2c	16	10	16	10
N3	4	2	3	2
Site				
Oropharynx	47	29	46	28
Sinuses and nasopharynx	6	4	7	4
Hypopharynx	10	6	9	5
Larynx	98	59	100	60
Miscellaneous	4	2	5	3
Bilateral neck irradiation				
Yes	111	67	110	66
No	54	33	57	34
Medical centre				
UMCG	43	26	43	26
VUMC	122	74	124	74

was carried out by using a shrinking action level correction protocol (SAL-protocol), using an electronic portal imaging device (EPID).

Patients with early glottic carcinoma were treated with a fractional dose of 2.5 Gy (5 times/week) up to a total dose of 60 Gy in 5 weeks or with a fraction dose of 2.0 Gy (5 or 6 times/week) up to a total dose of 66 Gy. These patients were only irradiated at the primary site.

Patients treated with concomitant CHRT were treated with conventional fractionation (2.0 Gy per fraction, 5 times per week up to 70 Gy in 7 weeks). In case of primary radiotherapy of the more advanced cases, which were considered not eligible for CHRT, an accelerated schedule with concomitant boost technique was used, either or not combined with cetuximab. These patients were generally treated with 6 fractions per week with a second fraction on Friday afternoon with a minimum interval of 6 h, up to a total dose of 70 Gy in 6 weeks. Most patients received bilateral elective irradiation of the neck nodes to a total dose of 46 Gy and a boost on the primary tumour and pathological lymph nodes to a total dose of 70 Gy. In some cases, radiotherapy only with conventional fractionation was used.

Contouring of organs at risk

Organs at risk (OARs) potentially involved in salivary function related symptoms were delineated according to the guidelines for OARs potentially involved in radiation-induced salivary dysfunction and xerostomia as described by Van de Water et al. [26], including the parotid, submandibular and sublingual glands, as well as the minor salivary glands located in the soft palate, the inner surface of the lower and upper lip and the minor salivary glands in the inner surface of the cheeks. All OARs were delineated

by an expert in head and neck radiation (JL). For this purpose, all planning-CT scans were transferred to the Pinnacle Treatment Planning System (TPS) (version 8.0 h, Philips Radiation Oncology Systems, Fitchburg, WI). After completing OARs contouring, all data were transferred to the VODCA platform (VODCA Company: viewer version 4.2.2. and database version 4.1.1). The VODCA platform is a software program which allows for dose distribution evaluation of different TPS's.

Dose distribution calculations

The dose distributions from the original treatment planning systems (Pinnacle, Masterplan, Eclipse, CadPlan) used were transferred to the VODCA platform in DICOM format. The original dose distributions in all aforementioned potential OARs could be reconstructed and DVHs could be generated.

Statistics

For the development of the predictive models for patient-rated xerostomia and sticky saliva, a multivariate logistic regression analysis was used with an extended bootstrapping technique and forward variable selection as described by El Naqa et al. [32]. In contrast to the El Naqa method, our method uses the likelihood criterion, instead of correlation measures. The average likelihood is calculated over all test datasets for each combination of variables. The model which gives the highest average likelihood was selected as the most predictive model.

Before carrying out the regression analysis, a correlation matrix was produced to check for high correlations between potential prognostic determinants, in particular between DVH-parameters. In case of Pearson correlation coefficients ≥ 0.8 between potential

prognostic determinants, these variables were combined into a single variable to avoid the problem of multicollinearity which may negatively affect the generalisability of the model. Finally, all DVH data were transferred to MATLAB (version R2009b) and connected to all other potential pre-treatment prognostic factors for each individual patient.

The variables initially included in the multivariate model are listed in Table 2. After reducing the number of variables based on the correlation coefficient analysis, a multivariate logistic regression with forward selection and an extended bootstrapping technique was carried out. We used 2000 bootstraps for each analysis. For every model order, the average likelihood of predictions was calculated and the number of variables selected with the highest average likelihood was selected for the definite predictive model for patient-rated xerostomia and sticky saliva.

After selecting the combination of variables with the highest performance in MATLAB, the analysis was repeated in SPSS for windows (version 16.0; SPSS, Chigaco, IL) using exactly the same dataset and selected variables. Adjusted Odd's ratios (ORs) and 95% confidence intervals (95% CI) were calculated in SPSS for the selected variables in the model. For each patient, predictive values (i.e., NTCP values) were calculated for each set of prognostic variables based on the regression coefficients according to the formula:

$$\text{NTCP} = (1 + e^{-S})^{-1}, \text{ in which}$$

$$S = \beta_0 + \sum_{i=1}^n \beta_i \cdot x_i$$

In SPSS, model performance was then determined by calculating the area under the curves (AUC) based on receiver operating characteristics.

Results

Variable reduction and dose distribution procedure

In order to reduce the number of variables in the model, we first produced a correlation matrix to identify DVH-parameters of all OARs that were strongly correlated (i.e., Pearson correlation coefficient ≥ 0.8) (Fig. 1). There was a very strong correlation between all DVH parameters within each OAR and the mean dose of that OAR. Therefore, we decided to only include the mean doses of all OARs in the multivariate model to prevent the problem of multicollinearity. In addition, we also found a very strong correlation between the mean dose in the ipsilateral and contralateral parotid, submandibular and sublingual glands and the ipsi- and contralateral glands in the cheek (Pearson $r > 0.8$). Therefore, we decided

Table 2

Univariate logistic regression coefficients for all possible predictors for xerostomia and sticky saliva.

Predictor	Xerostomia					Sticky saliva				
	β	OR	95% CI	p-value	AUC	β	OR	95% CI	p-value	AUC
Mean dose parotid glands (Gy)	0.06	1.06	1.04–1.08	<0.01	0.79	0.03	1.03	1.02–1.05	<0.01	0.69
Mean dose submandibular glands (Gy)	0.05	1.05	1.03–1.07	<0.01	0.75	0.04	1.04	1.02–1.05	<0.01	0.68
Mean dose sublingual glands (Gy)	0.02	1.02	1.01–1.04	<0.01	0.72	0.00	1.00	0.99–1.01	0.67	0.57
Mean dose cheeks (Gy)	0.04	1.04	1.02–1.07	<0.01	0.72	0.00	1.00	0.99–1.02	0.77	0.55
Mean dose inner surface lower lip (Gy)	0.02	1.02	1.00–1.05	0.07	0.67	−0.13	0.99	0.97–1.01	0.21	0.51
Mean dose inner surface upper lip (Gy)	0.03	1.03	1.00–1.07	0.06	0.65	−0.15	0.99	0.96–1.01	0.30	0.52
Mean dose soft palate (Gy)	0.03	1.03	1.02–1.05	<0.01	0.75	0.01	1.01	1.00–1.02	0.06	0.61
Sex	0.24	1.27	0.67–2.40	0.46	0.56	0.31	1.37	0.68–2.74	0.38	0.53
Age	0.01	1.01	0.98–1.04	0.54	0.51	0.03	1.03	1.00–1.06	0.06	0.57
Chemotherapy	0.93	2.53	1.15–5.58	0.02	0.58	0.21	1.24	0.59–2.59	0.57	0.52
Accelerated radiotherapy	−0.29	0.75	0.40–1.42	0.38	0.53	0.02	1.02	0.54–1.91	0.96	0.50
Baseline xerostomia score	1.01	2.75	1.39–5.47	<0.01	0.61	0.63	1.87	1.15–3.04	0.01	0.61
Baseline sticky saliva score	0.59	1.81	1.01–3.23	0.05	0.57	0.94	2.57	1.27–5.17	<0.01	0.59
Bilateral neck irradiation	1.80	6.06	2.90–12.66	<0.01	0.68	1.97	7.15	3.19–16.01	<0.01	0.69
Medical centre (UMCG vs. VUMC)	1.09	2.98	1.43–6.21	<0.01	0.60	1.54	4.67	2.0–10.9	<0.01	0.63

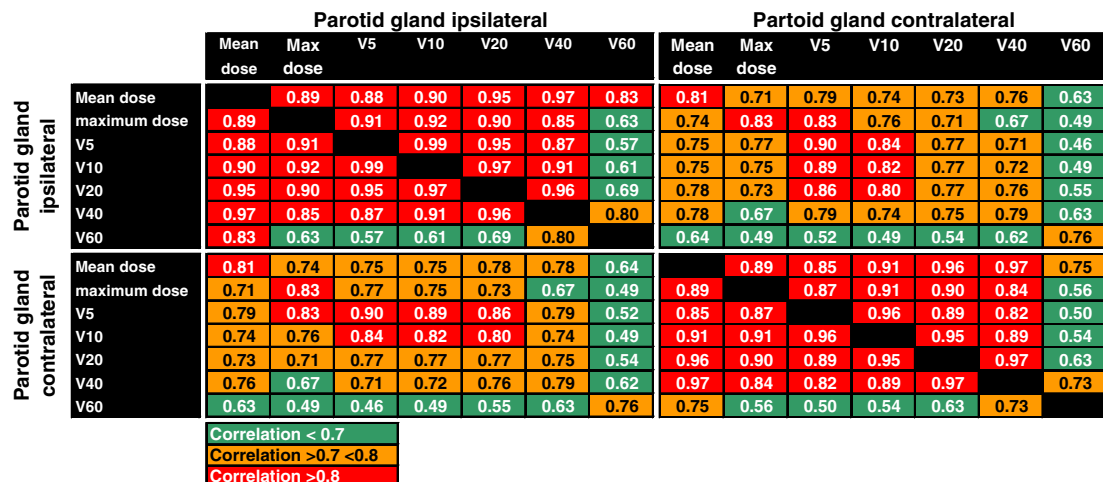


Fig. 1. Pearson correlation coefficients between the ipsi- and contralateral parotid gland. Part of the correlation matrix. Strong correlations between two variables (>0.8) are colored in red. Very strong correlations within and between ipsi- and contralateral salivary glands were observed and, therefore, analyses were carried out with pairs of ipsi- and contralateral glands, to avoid multicollinearity.

to use the mean dose in these ipsi- and contralateral glands as one single variable.

Appendix A includes the correlation matrix of all determinants entered in the multivariate analysis, the correlations between the mean dose to the parotid glands and submandibular glands was above 0.80 and also Pearson correlation between the parotid glands and dose to the soft palate was beyond 0.80 (0.87).

Prevalences of patient rated xerostomia and sticky saliva

At 6 months after treatment, 52% of the patients reported moderate to severe xerostomia. After 12, 18 and 24 months, 38%, 35% and 35%, respectively, reported moderate to severe xerostomia. At 6 months after treatment, 43% of the patients reported moderate to severe sticky saliva. At 12, 18 and 24 months after treatment, 28%, 33% and 27%, respectively reported moderate/severe sticky

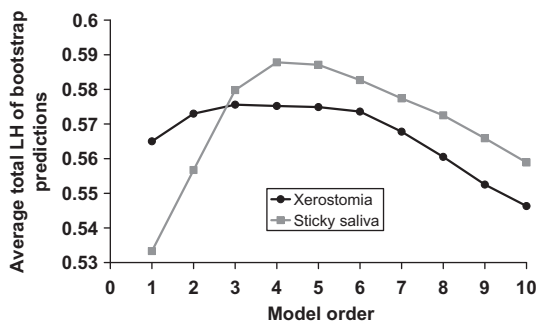


Fig. 2. Average likelihood for bootstrapping technique for each number of selected variables in the multivariate logistic regression analysis for each model order. Best model performance is observed with a model order with the highest average of total likelihood of bootstrap predictions. For, respectively, xerostomia and sticky saliva the best model performance was seen with three and four selected variables.

saliva. Additional analysis showed that the 6 month assessments were very predictive for these endpoints at subsequent time points. Therefore, we decided to use the 6 months assessments as primary outcome measure for the current analysis.

Xerostomia

In the univariate analysis, the mean dose in the parotid, submandibular, sublingual glands, the minor glands in the cheeks, the minor glands in the soft palate, chemotherapy, bilateral neck irradiation and baseline xerostomia and sticky saliva score (none versus a bit) and the treatment centre were significantly associated with patient-rated xerostomia 6 months after treatment (Table 2). Average likelihood of bootstrap prediction in the multivariate logistic regression analysis was optimal with a model consisting of three variables (Fig. 2). Increasing the number of variables to four did not further increase the average likelihood of the model compared to the 3-factor model.

The three variables selected were the mean dose to the parotid glands, age and baseline xerostomia (none versus a bit). AUC for this 3-factor model was 0.82 (95% CI 0.76–0.89). This model describes the relation for a mean dose of the parotid glands ranged from low dose to high dose (Table 3). The ORs for each of the 3 selected variables are shown in Table 4. The NTCP-value for each individual patient can be calculated by the following logistic regression formula:

$$\text{NTCP} = (1 + e^{-S})^{-1}, \text{ in which}$$

$$S = -5.27 + (\text{mean dose parotid gland} * 0.066) + (\text{age} * 0.050) + (\text{baseline xerostomia score} * 0.916)$$

Alternatively, the NTCP-value for each individual patient can be determined using the nomogram for xerostomia in Appendix B.

Table 3
Distributions of the mean dose for the selected organs at risk for the patient-rated xerostomia NTCP model (parotid glands) and for the NTCP model for patient-rated sticky saliva (submandibular glands and sublingual glands). The analysis for patient-rated xerostomia included 165 patients and for sticky saliva 167 patients.

Dose (Gy)	Mean dose parotid glands (n = 165)		Mean dose submandibular glands (n = 167)		Mean dose sublingual glands (n = 167)	
	Number of patients	%	Number of patients	%	Number of patients	%
0–10	45	27	25	15	80	48
10–20	9	5	13	8	12	7
20–30	35	21	9	5	7	4
30–40	29	18	11	7	11	7
40–50	13	8	29	17	17	10
50–60	11	7	19	11	14	8
60–70	23	14	31	19	19	11
>70	0	0	30	18	7	4

Table 4
Multivariate logistic regression model for patient-rated xerostomia and sticky saliva 6 months after treatment.

Predictor	β	p-value	Odds ratio	95% CI
<i>Xerostomia model</i>				
Mean dose parotid glands (Gy)	0.066	<0.001	1.07	1.05–1.09
Age (years)	0.050	0.014	1.05	1.01–1.09
Baseline xerostomia score (none vs. a bit)	0.916	0.024	2.50	1.13–5.55
Constant	–5.27	<0.001		
<i>Sticky saliva model</i>				
Mean dose submandibular glands (Gy)	0.091	<0.001	1.10	1.06–1.13
Age (years)	0.107	<0.001	1.11	1.06–1.17
Mean dose sublingual glands (Gy)	–0.041	<0.001	0.96	0.94–0.98
Baseline sticky saliva score (none vs. a bit)	1.218	0.006	3.38	1.42–8.06
Constant	–10.70	<0.001		

Sticky saliva

In the univariate analysis, the mean dose to the parotid and submandibular glands, bilateral neck irradiation, baseline sticky saliva score and xerostomia score (none versus a bit) and the treatment centre were significantly associated with patient-rated sticky saliva 6 months after treatment (Table 2). In the multivariate analysis with bootstrapping, the average likelihood was maximal with a model consisting of 4 variables (Fig. 2).

The four factor model included the following variables: the mean dose to the submandibular glands, age, the mean dose in the sublingual glands and sticky saliva at baseline. AUC for this four factor model was 0.84 (95% CI 0.78–0.90). This model describes the relation for a mean dose of the submandibular and sublingual glands ranged from low dose to high dose (Table 3). Odd's ratios for each selected variable are listed in Table 4.

A negative logistic regression coefficient (−0.041) was found for the mean dose of the sublingual glands and the OR was 0.96 for each Gray increase in dose (95% CI 0.94–0.98). Elderly patients suffered more from sticky saliva 6 months after treatment and patients with minor sticky saliva at baseline are more prone to develop moderate to severe sticky saliva as compared to those without any complaints of sticky saliva. The NTCP-value for each individual patient can be calculated by the following logistic regression formula:

$$\begin{aligned} \text{NTCP} &= (1 + e^{-S})^{-1}, \text{ in which} \\ S &= -10.70 + (\text{mean dose submandibular glands} * 0.091) \\ &+ (\text{age} * 0.107) + (\text{baseline sticky saliva score} * 1.218) \\ &+ (\text{mean dose sublingual glands} * -0.041) \end{aligned}$$

Alternatively, the NTCP-value for each individual patient can be determined out of the nomogram for sticky saliva in Appendix C.

Discussion

In this study, we investigated the significance of radiation dose distributions in the major and minor salivary glands in relation to patient-rated xerostomia and sticky saliva among patients treated with 3D-CRT. The results revealed that dose distributions in the minor salivary glands have limited significance for the development of patient-rated symptoms related to salivary dysfunction among patients treated with 3D-CRT. Besides dose distributions in the parotid glands and the submandibular glands, only the dose distributions in the sublingual glands were significantly associated with patient-rated sticky saliva. For both xerostomia and sticky saliva the risk was higher with increasing age and pre-existing minor complaints at baseline. This multivariate analysis of patient-rated xerostomia and sticky saliva clearly indicates that the estimation of the risk on developing these endpoints cannot be described by a simple univariate relationship between the dose in one OAR and these patient-rated endpoints.

In an earlier report, Jellema et al. reported on the results of a similar prospective study [31]. It should be noted that approximately two-third of the patients included in the study of Jellema were also used in this study. The main differences was that in the current study, we only included patients treated with primary (CH)RT while patients treated with surgery were excluded. The reason for this was that we were primarily interested in radiation-induced changes and preferred to only include patients with all salivary glands in situ. Another difference with the study of Jellema et al. was that instead of using the oral cavity dose as a surrogate for the dose in all individual minor glands in the cheeks, soft palate and lips, the dose distributions in all minor salivary glands were taken into account separately.

In the multivariate analysis the role of the minor salivary glands was limited and only the sublingual glands were selected as possible predictor for patient-rated sticky saliva. In the univariate analysis for xerostomia the minor salivary glands in the soft palate were significantly associated with the development of patient rated xerostomia. Similar results were found by Jellema et al. They also found a significant association between the doses in the oral cavity in the univariate analysis which, however, disappeared in the multivariate analysis if the mean parotid dose was entered in the multivariate model [31]. It should be stressed that these patients were all treated with 3D-CRT with consequently high correlations between the dose distribution parameters of the salivary glands included in the analysis.

We decided to analyse the parotid glands, submandibular glands, sublingual glands and the minor salivary glands separately because the content of saliva production of these glands is different from each other [16–22]. It is not unlikely that with IMRT, in which the dose to the parotid glands is significantly lower, the relative importance of the dose distributions to the submandibular glands and the minor glands increases. Therefore, the findings of the current study based on patients treated with 3D-CRT should be externally validated among those treated with more advanced techniques such as IMRT.

In the univariate analysis the treatment centre appeared as a possible independent predictor for patient-rated xerostomia and sticky saliva as well. The majority of patients treated in the University Medical Centre Groningen were treated with primary radiotherapy for laryngeal tumours and, therefore, had relatively low dose to the salivary glands located in the oral cavity. In contrast, patients treated in the VU Medical Centre were mainly included before 2007 and consisted of relatively more patients with oropharyngeal and oral cavity tumours. Therefore, the patients included from the VUMC had on average higher doses to the salivary glands. After correcting for these differences in case mix in the multivariate analysis, treatment centre itself was not significantly associated with any of the endpoints anymore.

This study investigated the relationship between patient-rated xerostomia and sticky saliva and the dose distributions in a variety of salivary glands as well as other potential predictive factors. Until now, most studies focused on the univariate relationship between dose and stimulated parotid flow [23–25]. Several NTCP models were used to describe this relationship. The Lyman–Kutcher–Burman model is currently the most commonly used NTCP model [33,34]. This model assumes a dose volume dependent and tolerance dose relation between a specific OAR and a specific endpoint. Other models also used information about dose distributions and fractionation [35,36]. El Naqa et al. were the first to publish a study describing a model that was not only based on dose volume characteristics, but also took other potential prognostic clinical factors into account [32].

Some studies showed discrepancies between different endpoints related to salivary dysfunction [13,31,37–39]. Kam et al. showed significant differences in stimulated parotid salivary flow, whole saliva flow and physician-rated xerostomia according to the RTOG criteria in a patient population treated for head and neck cancer with IMRT compared with a patient population treated with two-dimensional radiotherapy (2D-RT). However, no significant difference in patient-rated xerostomia was found [38]. These findings suggest that patient-rated xerostomia can not only be explained by changes in the parotid flow due to the radiation of the parotid glands, but other clinical factors are of importance as well.

The parotid glands are responsible for the serous secretion of saliva, while the other major and minor salivary glands produce saliva with a (much) higher viscosity [16,18,40,41]. Radiation damage of the acinar cells in the parotid glands diminish the saliva production [18,8]. Due to irradiation of the submandibular glands and

parotid glands the serous secretion of saliva is diminished more than the mucus secretion [8,17,18,40,41]. The viscosity and pH of the saliva will change in such a way that patients will be more aware of sticky saliva [8,17,18,40,41].

An important finding was the inverse relationship between the mean dose to the sublingual glands and patient-rated sticky saliva. A possible explanation for this apparent protective effect of irradiation could be related to the composition of the saliva produced by the sublingual glands. The sublingual glands only produce highly viscous mucous saliva [18], while irradiation of the parotid and submandibular glands will mainly reduce production of serous saliva production. Irradiation of the latter major glands with sparing of the sublingual glands may increase the ratio between mucous saliva and serous saliva, resulting in higher viscosity of saliva and thus more sticky saliva. Irradiation to the sublingual glands will reduce the mucous saliva production resulting in a more balanced ratio between mucous and serous saliva production.

Another important finding was that elderly patients have a higher probability of suffering from xerostomia and sticky saliva than younger patients. This is completely in agreement with the fact that the prevalence of hyposalivation and xerostomia and sticky saliva in a healthy population is higher in patients beyond 50 years [42]. Older patients are more likely to use medication and to have co-morbidity that may influence and reduce the saliva production at rest [43,44]. Therefore, older patients are more prone to develop xerostomia and sticky saliva due to reduced secretory reserve [45]. Only small influences on the secretion of saliva of the salivary glands, like medication and radiation dose, are needed to develop hyposalivation [45,46].

The development of the NTCP models for patient-rated xerostomia and sticky saliva in patients treated for head and neck cancer with 3D-CRT was the first study in the four-step ALLEGRO approach to build validated predictive models which can be used in the estimation which patients will benefit from new radiation techniques. The next step in the ALLEGRO project will be the validation of these models in a population treated with IMRT. It is not self-evident that predictive models developed among patients treated with 3D-CRT are per definition valid among patients treated with other radiation delivery techniques, such as IMRT, due to the fact that the dose distributions in the salivary glands will show much more variability with IMRT. This was very nicely illustrated by Dijkema et al. who showed that the NTCP model for salivary flow among patients treated with 3D-CRT differed from that among patients treated with IMRT [47]. Moreover, with IMRT, the correlation between the dose distributions in the paired glands will differ much more, which means that both glands will probably be selected for inclusion in the multivariate analysis, which was not the case in the present study.

Recently, we reported on the validation of a new xerostomia questionnaire (the Groningen Radiotherapy-Induced Xerostomia questionnaire (GRIX)), which can distinguish between patient-rated xerostomia and sticky saliva in different situations, such as complaints during the day or during the night [48]. As the minor salivary glands and submandibular glands play a more important role in production of saliva than the parotid glands during the night, it could be hypothesized that predictive models for these complaints change in correspondence with circadian rhythms of salivary productions of the different salivary glands [18].

In conclusion, we developed predictive models for patient-rated xerostomia and sticky saliva in patients treated with 3D-CRT for head and neck cancer, using multivariate bootstrap logistic regression analysis. The results of our study illustrate that these endpoints cannot be predicted with one simple relationship between the dose distribution in an OAR and an endpoint but that other factors than DVH parameters are important as well. However, the role of the dose distributions to the minor salivary glands (the

sublingual glands, the salivary glands in the soft palate and in the inner surface of the cheeks and lips) on the development of these factors appears limited when treated with 3D-CRT. These results should be validated among patients treated with IMRT.

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Appendix. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.radonc.2011.05.010.

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